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EXAMINER	
GODDARD, LAURA B	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,162	SOWA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-24* is/are pending in the application.

4a) Of the above claim(s) *18-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/9/03, 3/7/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed November 30, 2005 in response to the Office Action of November 1, 2005 is acknowledged. Applicant elected with traverse Group 1 (claims 6-in-part drawn to identification of an agent alone, 7, 8-in-part drawn to GAL4, 9-in-part drawn to luciferase, 10-in-part drawn to luciferase, 11-17). Applicants perfected the priority claim upon submission of a certified translation of the priority document JP 11-77350, dated March 23, 1999, to over come the Sowa et al., 1999 reference.

However, the inventions listed as Groups 1- 32 still do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions are distinct, each from the other because of the following reasons: A national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said

process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group 1 will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

Given the above, the issue remains the same, the claimed inventions do not have unity of invention and therefore in the interest of compact prosecution, Group 1, as elected, will be examined and for the reasons set forth above, restriction to the claimed invention is proper.

Claims 6-24 are pending. Claims 18-24 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 6-17 as drawn to a heterologous protein GAL4 and a reporter gene encoding luciferase are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 6-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a method of identifying an agent having cellular anti-proliferation activity, comprising: providing a cell having (a) a first vector comprising a first regulatory sequence operably linked to a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) a **fragment thereof of Sp3 having transcriptional activation activity** and (ii) a DNA binding domain of a heterologous protein, GAL4; and (b) a second vector comprising a target binding sequence for the DNA binding domain of the fusion protein operably linked to a reporter gene encoding luciferase; contacting the cell with a test agent; and selecting a test agent that increases the expression of the reporter gene compared to a control.

The specification discloses a single class of fragments comprising the TSA-responsive domain of Sp3 that have transcriptional activation activity, that is, a class of fragments that comprise at least one glutamine-rich region of TSA-responsive domain of Sp3 and lacks at least amino acid residues 495-517, 525-547, 555-575 of the Zinc finger region, that would be expected to function as claimed to predictably identify an activator of TSA-dependent Sp3 transcription. The specification does not disclose any other Sp3 fragments having transcriptional activity as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of **"a fragment of Sp3 having transcriptional activation activity".** Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated,

> does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A

disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an Sp3 fragment having transcriptional activation activity, per Lilly by structurally describing representative Sp3 fragments or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an Sp3 fragment having transcriptional activation activity useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses a single class of fragments comprising the TSA-responsive domain of Sp3 that have transcriptional activation activity, that is, a class of fragments that comprise at least one glutamine-rich region of TSA-responsive domain of Sp3 and lacks at least amino acid residues 495-517, 525-547, 555-575 of the Zinc finger region, this does not provide a description of the broadly claimed Sp3 fragments that would satisfy the standard set out in Enzo because the specification provides only a single set of structural features coupled to the claimed function but fails to describe structure/function relationships of the other broadly claimed members of the genus. Other than the single class of

fragments set forth above, the specification describes the instant fragments only by function.

Further, the specification also fails to describe Sp3 fragments by the test set out in Lilly because the specification describes only a single class of fragments comprising the TSA-responsive domain of Sp3 that have transcriptional activation activity, that is, a class of fragments that comprise at least one glutamine-rich region of TSA-responsive domain of Sp3 and lacks at least amino acid residues 495-517, 525-547, 555-575 of the Zinc finger region. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of Sp3 fragments that is required to practice the claimed invention. Since the specification fails to adequately describe the product critical to the claimed method of identifying an agent having cellular anti-proliferation activity by activating Sp3 transcription, it also fails to adequately describe the method.

Note: If applicant were to overcome the preceding rejection (s) under 35 U.S.C. 112, first paragraph, the following claims would still be rejected under 35 U.S.C. 112, first paragraph, scope of enablement:

3. Claims 6-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an agent having cellular anti-proliferation activity, comprising: providing a cell having (a) a first vector comprising a first regulatory sequence operably linked to a nucleic acid sequence encoding a fusion

protein, wherein the fusion protein comprises (i) **a fragment of human Sp3 comprising at least one glutamine-rich region of TSA-responsive domain of Sp3 and lacking at least amino acid residues 495-517, 525-547, 555-575 of the Zinc finger region, and having transcriptional activation activity** does not reasonably provide enablement for a method of identifying an agent having cellular anti-proliferation activity, comprising: providing a cell having (a) a first vector comprising a first regulatory sequence operably linked to a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) **a fragment of Sp3 having transcriptional activation activity**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of identifying an agent having cellular anti-proliferation activity, comprising: providing a cell having (a) a first vector comprising a first regulatory sequence operably linked to a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) **a fragment of Sp3 having transcriptional activation activity** and (ii) a DNA binding domain of a heterologous protein; and (b) a second vector comprising a target binding sequence for the DNA binding domain of the fusion protein operably linked to a reporter gene; contacting the cell with a test agent; and selecting a test agent that increases the expression of the reporter gene compared to a control. This means the claims are drawn to a method wherein the fusion protein comprises **any Sp3 from any species** and **any fragment of any Sp3** having transcriptional activity.

The specification discloses Sp3 is involved in the transcriptional activation of p/21/WAF1/Cip1 by Trichostatin A (TSA) (p. 4, lines 16-17; Example 4) and that TSA, a known histone deacetylase (HDAC) inhibitor, has a tumor-suppressing effect (p. 3, lines 22-23). The specification discloses "the method of this invention for screening an anticancer agent is based on the finding by the inventors that Sp3 is involved in the signal transduction leading to the expression of antitumor effects in response to a TSA stimulus" (p. 5. lines 22-24).

The specification discloses that transcriptional activation in response to a TSA stimulus could occur if at least one of the two glutamine-rich domains contained in the Sp3 transcription activation domain was present (p. 4, lines 10-14). Example 3 of the specification discloses the identification of the TSA responsive domain of Sp3, wherein the transcriptional induction by TSA seems to require the presence of at least one of the two glutamine-rich domains in the Sp3 transcriptional domain, and the 80-160 region of Sp3 may contain part of an important region for TSA mediated transcriptional induction (p. 19, lines 26-31 to p. 20, lines 1-4; Figure 3). The specification discloses that the region having transcriptional activation capacity of the Sp3 protein is not limited as long as it contains a region capable of transcriptional activation in response to a TSA stimulus and that such a region desirably comprises at least a part of the transcription activation domain and lacks at least part of the DNA binding domain (zinc finger region). The specification discloses that the claimed screening method is possible even in the presence of the DNA binding region derived from Sp3 but **the presence of this DNA binding domain or zinc finger is not desirable because a fusion protein**

comprising this region can bind to various endogenous Sp1 binding sequences. Further, the specification discloses that in the case of **human Sp3 protein**, a desirable region **comprises at least one of the two glutamine-rich regions (amino acids 495-517, 525-547, and 555-575), and lacks at least part of the zinc finger region (amino acids 495-517, 525-547, and 555-575)** (p. 7, lines 5-17). The specification does not disclose any other Sp3 or fragments thereof having transcriptional activity at any response element other than the TSA element that would function in the claimed method as broadly encompassed in the claims.

The claims are not enabled because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. Thus, the claims are not enabled for a method of identifying an agent having cellular anti-proliferation activity comprising a vector encoding a fusion protein comprising **any fragment Sp3** having transcriptional activity. In view of the disclosure of the specification that the presence of the Zinc binding domain is not desirable in the fusion protein because this region can bind to various endogenous Sp1 binding sequences, it would be expected that the inclusion of the specifically cited residues in the fusion protein would lead to identification of numerous species that are not associated with Sp3 transcription and thus it could not be predicted which or how many of the identified species would in fact be affecting Sp3 transcription and which would function as claimed.

Further, Majello et al (J Biological Chemistry, 1997, 272:4021-4026, IDS) teach that Sp3 is a bifunctional transcriptional regulator containing independent modular

repressor and activator domains. The activator potential of Sp3 is distributed over an extensive glutamine-rich N-terminal region and the negative regulatory function has been mapped 5' of the zinc finger region. The reference teaches that the Sp3-repression ability is strikingly dependent upon the context of the Sp3 DNA-binding sites present in the reported promoters. Sp3 functions as a repressor when it is bound to the promoter through multiple DNA-binding sites. Sp3 is an activator when it is targeted to the promoter via a single binding site (p. 4021, col. 2). The reference teaches that different allosteric changes may occur depending upon the context of DNA-binding sites, allowing mutual exclusive interactions between diverse Sp3 domains and putative cofactors leading to a different transcription response (p. 4025, col. 2). Finally, the reference teaches that Sp3 repression ability is also dependent upon the cellular context (p. 4025, col. 2).

Considering the disclosure of the specification and teachings of Majello et al, it would be expected that an Sp3 fragment which includes a zinc finger region would bind Sp1 binding sequences instead of Sp3, and that Sp3 can potentially function as a transcriptional repressor instead of an activator depending upon the DNA binding domains present in the promoter region, hence, the claimed method would not function without transcription activated by Sp3. A method of identifying an agent having cellular anti-proliferation activity comprising a vector encoding a fusion protein that comprises an Sp3 or Sp3 fragment containing the zinc finger region or several DNA binding domains, or no glutamine-rich regions would not predictably function as claimed.

Further, regarding a method comprising a fusion protein comprising an Sp3 from any species, Kolell et al (Mol Biol Evl, 2002, 19:216-222) teach that Sp3 proteins from different species are not 100% homologous. The Sp3 proteins from a fish and mouse are related to human Sp3 but comprises different sequences as shown in the evolutionary relationships of Figures 2, 3, 5, and 6. The reference teaches that when comparing a "B domain" of Sp3 between fish and mammalian proteins, the fish Sp3 did not group with the mammalian Sp3 (Figure 5; p. 220, col. 1). It cannot be predicted that an Sp3 from a mouse, fish, or any species that differs in sequence from human Sp3 would function in the method as claimed. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al

(J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Despite the homology between the Sp3 protein of different species it cannot be predicted, based on the information in the specification, what affect the differences between the Sp3 proteins have on the function of the protein, particularly relating to the transcriptional activation activities in response to an agent such as TSA. Thus, the claims are not enabled for a method of identifying an agent having cellular

anti-proliferation activity comprising a vector encoding a fusion protein comprising **any Sp3 or a fragment of any Sp3** having transcriptional activity.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that the claimed method of identifying an agent having cellular anti-proliferation activity will predictably function as disclosed. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Note: If applicant were to overcome the preceding rejection (s) under 35 U.S.C. 112, first paragraph, the following claims would still be rejected under 35 U.S.C. 112, first paragraph, scope of enablement:

4. Claims 6-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method of identifying an agent that activates the Sp3 TSA response element**, does not reasonably provide enablement for **a method of identifying an agent having cellular anti-proliferation activity**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of identifying an agent having cellular anti-proliferation activity, comprising: providing a cell having (a) a first vector comprising a

first regulatory sequence operably linked to a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) Sp3 or a fragment thereof having transcriptional activation activity and (ii) a DNA binding domain of a heterologous protein; and (b) a second vector comprising a target binding sequence for the DNA binding domain of the fusion protein operably linked to a reporter gene; contacting the cell with a test agent; and selecting a test agent that increases the expression of the reporter gene compared to a control, this means the claims are drawn to a method of identifying agents having cellular anti-proliferation activity based on the activation of Sp3-dependent transcription.

The specification discloses Sp3 is involved in the transcriptional activation of p/21/WAF1/Cip1 by Trichostatin A (TSA) (p. 4, lines 16-17; Example 4) and that TSA, a known histone deacetylase (HDAC) inhibitor, has a tumor-suppressing effect (p. 3, lines 22-23). The specification discloses that sodium butyrate and TSA activated p/21/WAF1/Cip1 gene promoter through the Sp1 binding sequence (p. 2, lines 11-12). The specification discloses "the inventors thought it might be possible to screen an anticancer agent targeting a novel molecule by identifying a new molecule involved in the signal transduction leading to the activation of the p21/WAF1/Cip1 promoter in response to a TSA stimulus" (p. 3, lines 25-28) and "the method of this invention for screening an anticancer agent is based on the finding by the inventors that Sp3 is involved in the signal transduction leading to the expression of antitumor effects in response to a TSA stimulus" (p. 5. lines 22-24). The specification further discloses that it is thought that the treatment and prevention of cancer are possible by enhancing the

activity of Sp3 that suppresses cell neoplasia (p. 5, lines 19-21). However, the claims are not enabled because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. It is clear that TSA has known anti-tumor effects and that it activates Sp3 under certain conditions (p. 7, lines 4-15; Example 3), however, it is not clear how the identification of any agent that activates Sp3 predictably identifies an agent having cellular anti-proliferation activity. Thus, the claims are not enabled for a method of identifying an agent having cellular anti-proliferation activity.

Black et al (J of Cellular Physiology, 2001, 188:143-160) teach that 'Sp1 site'-dependent transcription is involved in many signal transduction pathways linked to cancer, and this role in signal transduction has been shown to directly impinge on transformation. For example, Sp1 and Sp3 DNA-binding activity are increased in epithelial tumors compared with papillomas, indicating increased activity of these factors contributes to tumor progression in skin, however, as seen with regulation of transcription, the role of these proteins in cancer is context-dependent (p. 147, col. 2). Black et al teach overlapping DNA binding specificities but different transcriptional properties of related Sp proteins. Black et al teach that Sp3 has been found to activate or repress transcription, dependent on the cell line or promoter examined, meaning the transcriptional property of Sp3 is context-dependent (p. 145, col. 1). Black et al teach that studies indicate that, depending on the promoter, upregulation of 'Sp1 site'-dependent transcription can be related to positive or negative changes in cell growth (p. 144, col. 1). Overlapping DNA binding specificities at 'Sp1-sites' for Sp factors yet

different transcriptional properties of Sp factors demonstrate the differential expression of positively and negatively acting Sp and related proteins. For example, an Sp3 protein with an intact DNA binding domain can compete with Sp1 for promoter binding and regulate transcription at 'Sp1 site'-containing promoters by inhibiting promoter activity in an Sp1-dependent manner. Competition for promoter binding is a viable means for regulating transcription at 'Sp1 site'-containing promoters (p. 145, col. 2). Black et al teach that repressive, shorter isoforms of Sp3 can also inhibit Sp1/Sp3-dependent transcription by DNA binding-independent mechanisms that appears to involve competition for components of the basal transcription machinery (p. 145, col. 2). The teachings of Black et al indicate that the role of Sp3 in cell growth or growth inhibition is context-dependent and that many factors play a role in the cellular pathways involving 'Sp1 site'-containing promoters. Considering the teachings of Black et al, it could not be predicted that an agent that increases Sp3 transcriptional activity would predictably identify that the agent has cellular anti-proliferative activity.

It is clear that the activation of the p21/WAF1/Cip1 promoter initiates the binding and inhibition of cyclin/cyclin-dependent kinase complexes resulting in cell cycle arrest, but the detection of the activation of the p21/WAF1/Cip1 promoter or the detection of cell growth inhibition is not detected in the claimed method. Considering the teachings of Black et al, there are many factors involved in the activation or repression of promoters containing 'Sp1 sites' such as p21/WAF1/Cip1, and the activity of Sp3 is extremely context-dependent, hence, it could not be predicted that that an agent that

transcriptionally activates Sp3 in using the claimed method could predictably identify an agent having cellular anti-proliferative activity.

With regards to identifying an agent having cellular anti-proliferation activity or an agent for the treatment or prevention of cancer as contemplated by the specification, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that a method of identifying an agent having cellular anti-proliferation activity based on the activation of Sp3 could be predictably used to identify an anti-cancer agent for cancer therapeutic strategies as inferred by the claim and as contemplated by the specification. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has

been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that a method of identifying an agent having cellular anti-proliferation activity based on the activation of Sp3 could be predictably used to identify an anti-cancer agent for cancer therapeutic strategies as inferred by the claim and as contemplated by the specification. In addition, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The agent may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the agent. In addition, the agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the agent has no effect, circulation into the target area may be insufficient to carry the agent and a large enough local concentration may not

be established.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as inferred and contemplated by the specification with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly claimed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER